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Original Article

Chronotype and Daytime Sleepiness in Women with Hashimoto's Thyroiditis: A Cross-sectional Pilot Study

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Abstract

Background and objectives: Hashimoto's thyroiditis (HT), an autoimmune disease with a prevalence 2–7 times higher in women than in men, is associated with daytime sleepiness. The present study aimed to test the hypothesis that thyroid function is associated with chronotype and daytime sleepiness in women with HT.

Methods: This retrospective cross-sectional study included women with confirmed HT. Demographic, clinical and laboratory data were collected. The reduced Morningness-Eveningness Questionnaire (rMEQ) and the Epworth Sleepiness Scale (ESS) were used to assess chronotype and daytime sleepiness, respectively. Based on rMEQ, women were categorized as having a morning (≥18), intermediate (12–17) or evening (≤11) chronotype. Based on ESS, women were categorized as having normal or increased daytime sleepiness.

Results: Overall, 106 women, aged 43 ± 12 years, were included. Most had normal daytime sleepiness (68.9%), and the majority had an intermediate chronotype (61.3%), while only one had a morning chronotype (0.9%). Age was significantly associated with chronotype (P = 0.026). There was a significant association between chronotype and thyroglobulin antibodies (TgAb, P = 0.012). Free triiodothyronine (fT3) levels were significantly higher in women with an evening chronotype than in those with an intermediate chronotype (P = 0.045; OR = 0.500; 95% CI 0.25–0.98). Daytime sleepiness was significantly associated with TgAb (P = 0.016) and thyroid-stimulating hormone (TSH, P = 0.040). TgAb levels were significantly higher in women with increased daytime sleepiness (P = 0.049, OR = 1.003, 95% CI 1.00–1.01) than in those with normal daytime sleepiness.

Conclusions: Approximately one-third of women have an evening chronotype, and approximately one-third had increased daytime sleepiness. TgAb, fT3, and TSH are associated with daytime sleepiness or chronotype in women with HT. Further investigation is required for the underlying mechanisms.

Introduction

Hashimoto's thyroiditis (HT) was first described by Japanese doctor and medical scientist Haraku Hashimoto (1881–1934) in 1912 as "struma lymphomatosa," meaning an enlarged thyroid gland infiltrated with lymphocytes.[1] This most prevalent autoimmune disease, as well as one of the most common endocrine disorders, is usually referred to as autoimmune chronic thyroiditis. It is the most frequent cause of primary hypothyroidism in iodine-sufficient areas of the world, but clinical presentation, besides hypothyroidism, can also include thyrotoxicosis and euthyroidism.[2]

The prevalence of HT differs considerably across the general population depending on socioeconomic, environmental, genetic, and other factors. The global prevalence of HT ranges from 5% to 10%, with areas reporting prevalences as high as >20% and as low as <0.5%.[3] The prevalence is 2–7 times higher in women than in men, due to genetic susceptibility and differences in microbiome

Keywords: Chronobiology disorders; Circadian rhythm; Hypothyroidism; Morningness-Eveningness; Sleep disorders; Circadian rhythm.

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composition.[4–7]

Laboratory findings often include reduced free thyroxine (fT4), elevated thyroid-stimulating hormone (TSH), and normal or decreased free triiodothyronine (fT3). However, a substantial proportion of individuals with HT remain euthyroid or have subclinical hypothyroidism.[8] The pathophysiological basis of the disease involves dysregulation of humoral immunity, characterized by increased production of antibodies to thyroid peroxidase (TPOAb) and thyroglobulin (TgAb), as well as cell-mediated immune processes that promote apoptosis of thyroid follicular cells.[9] Lymphocytic infiltration and follicular destruction are common pathological findings that result in impaired hormone secretion and metabolic disturbances, such as elevated lipoproteins and reduced iron levels.[10,11] Iron deficiency is caused by impaired absorption, poor nutritional status, chronic inflammation due to the activation of pro-inflammatory cytokines, and heavy menstrual bleeding. Anemia is secondary and known as anemia of chronic disease. As well as hyperlipidemia, it may resolve with levothyroxine (LT4) replacement therapy, except in cases of genetically or metabolically driven disorders. The diagnosis of HT is based on clinical presentation, thyroid ultrasonography, and elevated TPOAb and/or TgAb concentrations.[2,12] TPOAb are present in approximately 95% of affected individuals,[13,14] whereas TgAb are considered less reliable, occurring in 60–80% of cases.[15]

The hypothalamic–pituitary–thyroid (HPT) axis is regulated by the circadian clock through the suprachiasmatic nucleus (SCN) in the hypothalamus. The circadian rhythm regulates sleep–wake cycles and many behavioral and physiological processes. Disturbances of circadian rhythm are associated with inflammatory processes and autoimmune diseases.[16] Chronotype, defined as an individual's preference for sleep–wake patterns, is determined by genetic, environmental, and lifestyle factors.[17] It is typically assessed using the Morningness–Eveningness Questionnaire (MEQ) or the Munich Chronotype Questionnaire.[17,18] Chronotype, or an individual's circadian preference, determines when a person is naturally most alert and functional during the day and reflects the assessment of biological rhythms. In contrast, the Epworth Sleepiness Scale (ESS) measures daytime sleepiness, or the subjective likelihood of falling asleep in everyday situations. It assesses how sleepy a person is during the day regardless of when they sleep, as well as the consequences of insufficient or poor-quality sleep.[19] Chronotype reflects circadian clock activity under the influence of the SCN and is associated with sleep disorders, metabolic and autoimmune diseases, malignancies, and premature aging.[20] Altered diurnal TSH secretion profiles have been reported in individuals with hypothyroidism and hyperthyroidism.[21] The evening chronotype is associated with poorer sleep quality, metabolic disorders, and immune dysregulation and may be linked to elevated TSH and increased risk for hypothyroidism.[22,23]

Daytime sleepiness, a common symptom of HT,[24–26] reflects sleep disturbance and circadian rhythm disruption and is assessed using the ESS.[27] Adequate and continuous sleep is essential for cognitive function and overall health, while reduced sleep duration and circadian desynchronization increase the risk of metabolic and cardiovascular disorders.[28] Sleep disturbances, which are highly prevalent in the general population,[29] impair quality of life and often accompany thyroid disorders.[30,31] Sleep is associated with characteristic changes in endocrine activity, including alterations in the HPT axis.[29,32] Furthermore, sleep has been shown to modulate immune processes, resulting in significant circadian variations in immunological parameters.[33] Sleep regulation represents a complex neuroendocrine process that affects many vital functions.[34,35]

Disturbance of the circadian regulation of the endocrine system is a crucial mechanism contributing to adverse health outcomes.[36,37] Shorter sleep duration may increase the risk of subclinical hypothyroidism,[34,38] while subclinical hypothyroidism may also lead to reduced sleep duration.[34,39] Subclinical hypothyroidism, defined by elevated TSH with normal fT3 and fT4 levels, is associated with poorer sleep quality and shorter sleep duration.[39] It should be noted that daytime sleepiness is common in autoimmune thyroid diseases, including HT, due to metabolic and systemic effects, and abnormal thyroid function may further disrupt sleep architecture. Therefore, we hypothesized that thyroid function is associated with chronotype and daytime sleepiness in women with HT. The present study aimed to test this hypothesis.

Materials and methods

Study participants

The study included women with HT who were diagnosed with hypothyroidism and who had elevated TSH and/or decreased thyroid hormones (fT3 and fT4), and/or elevated TPOAb and TgAb.[40,41] The inclusion criteria were age over 18 years and clinically, ultrasonographically, and laboratory-confirmed HT (elevated TPOAb and TgAb, or elevated TPOAb or elevated TgAb). Exclusion criteria were age under 18 years; euthyroidism; pregnancy; type 2 diabetes mellitus; malignant diseases; other autoimmune diseases; acute or chronic infectious conditions; oral supplementation with iodine, iron, selenium, zinc, myoinositol, magnesium, B complex vitamins, or vitamin D; treatment with hypolipidemic drugs; obstructive sleep apnea; or other chronic or neurological disorders associated with sleep disturbances (Fig. 1). All analyses were conducted at the same institution using the same laboratory method to ensure data comparability. Medical history data included age, sex, height, weight, body mass index (BMI), and LT4 replacement therapy, which was recorded as a binary variable: LT4 use or non-use. Thyroid hormone and antibody measurements were performed at the same time of day. For all women on LT4 therapy, blood was drawn before the daily LT4 dose. Based on BMI, women were categorized as normal weight (BMI < 25 kg/m^2), overweight (BMI 25–29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2).

Ethical consideration

This retrospective cross-sectional study included a group of women (N = 106) diagnosed with HT at a single center at the Leptir Clinic in Zagreb between November 2023 and February 2024 who met the inclusion criteria. It was approved by the Ethics Committee of the Leptir Polyclinic Zagreb (No. 25-10-6-12/23) and the Ethics Committee of the Faculty of Dental Medicine and Health, Osijek, Josip Juraj Strossmayer University, Osijek, Croatia (No. 2158/97-97-10-24-03). All patients signed written informed consent agreeing to complete the questionnaire and allow the use of their medical data (e.g., biochemical analytes) for the study. The study was conducted in accordance with the principles of good clinical practice, the Declaration of Helsinki (2013 revision), and all subsequent amendments.

Biochemical analyses

Laboratory data included measurements of total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), iron, vitamin D, TPOAb, TgAb, fT3, fT4, and TSH (Abbott, Chicago, IL, USA). Concentrations of TgAb, TPOAb, fT3, fT4, TSH, and vitamin D were determined by chemilumines-

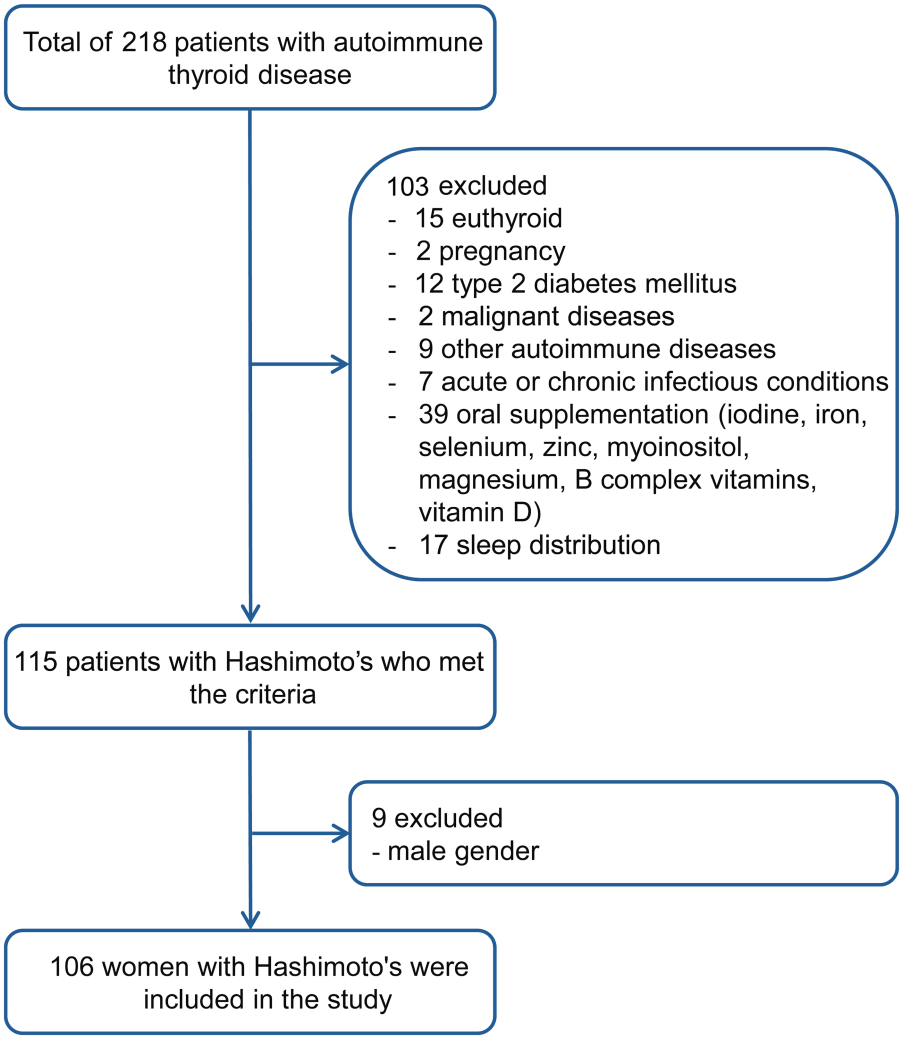

Fig. 1. Flowchart of patient selection.

cent microparticle immunoassay using Abbott reagent kits on an automated Alinity i chemiluminescent analyzer (Abbott Laboratories, Chicago, IL, USA) with reference values for TgAb < 115 kIU/L, for TPOAb < 34 kIU/L, for fT3 3.95 to 6.8 pmol/L, for fT4 12 to 22 pmol/L, for TSH 0.27 to 4.2 mU/L, and for vitamin D 50 to 200 nmol/L. All other analytes were measured on an automated Alinity c analyzer (Abbott Laboratories, Chicago, IL, USA). Reference values for the analytes were: cholesterol <5 mmol/L, triglycerides <1.7 mmol/L, HDL >1.2 mmol/L, LDL <3 mmol/L, and iron 8 to 30 µmol/L.

Questionnaire

Women completed a self-administered questionnaire with two sections, supervised by DK to minimize variability. The first section included the reduced Morningness-Eveningness Questionnaire (rMEQ). Horne and Östberg developed the MEQ, which is the most widely used measure of morningness.[42] Adan and Almirall later developed the reduced version (rMEQ).[43] This scale consists of five items, and the correlation between the rMEQ and the MEQ ranges from satisfactory to excellent (r = 0.69–0.90).[44] The total rMEQ score, calculated by summing the responses to each item, ranges from 4 to 25, with higher scores indicating a preference for morningness. In this study, the rMEQ items were taken from the Croatian translation of the MEQ.[45] Cut-off values for chronotype were: morning type (≥18), intermediate type (12–17), and evening type (≤11).

The second section of the questionnaire included the ESS,[27,46] one of the most widely used instruments in sleep medicine. The ESS has been validated and translated into Croatian and is available on the Mapi Research Trust website. It has also been used in previous studies.[47] Each woman's ESS score was the sum of her responses to the eight items (range 0–24), which were classified into four categories of daytime sleepiness, ranging from normal to severe. Cut-off values for daytime sleepiness were: normal sleepiness (0–10), mild sleepiness (11–14), moderate sleepiness (15–17), and severe sleepiness (≥18), where mild, moderate, and severe sleepiness indicate increased daytime sleepiness.

Statistical analyses

The G*Power program (version 3.1.9.4, Germany) was used to calculate the study's power.[48] At a significance level of $\alpha = 0.05$ and a sample size of 106 women, the achieved power was 67.3%.

Table 1. The association between general and biochemical data with chronotype and daytime sleepiness in women with HT (N = 106)

	Chronotype		Daytime sleepiness	
	χ^2	*P**	χ^2	*P**
Age (years)	467.677	0.026	704.434	0.808
BMI (kg/m^2)	1,046.834	0.273	1,871.510	0.277
LT4	14.344	0.158	24.055	0.153
Cholesterol (mmol/L)	406.983	0.394	741.123	0.285
Triglycerides (mmol/L)	179.909	0.843	324.131	0.913
HDL (mmol/L)	192.106	0.913	431.710	0.105
LDL (mmol/L)	372.704	0.596	652.183	0.804
Iron (µmol/L)	257.220	0.074	621.922	0.090
Vitamin D (nmol/L)	755.141	0.809	1,473.808	0.165
TPOAb (kIU/L)	910.696	0.668	1,643.753	0.697
TgAb (kIU/L)	829.006	0.012	1,445.717	0.016
TSH (mU/L)	772.349	0.086	1,386.497	0.040
fT3 (pmol/L)	241.286	0.954	494.338	0.612
fT4 (pmol/L)	575.600	0.899	1,140.356	0.299

**P*-values for χ^2-test. BMI, body mass index; fT3, free triiodothyronine; fT4, free thyroxine; HDL, high-density lipoprotein; HT, Hashimoto's thyroiditis; LDL, low-density lipoprotein; LT4, levothyroxine; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone (thyrotropin).

Data were analyzed using SPSS statistical software (version 26.0; SPSS Inc., Chicago, IL, USA). The normality of the data distribution was tested using the Shapiro–Wilk test. The results showed that all analyzed variables deviated significantly from normality. Variables were classified as binary or numerical, and descriptive statistical analyses were performed. Data were presented as median (IQR), minimum and maximum values, or absolute and relative frequencies. Differences in numerical variables between the two groups were tested using the Mann–Whitney U test. The association between numerical variables and rMEQ and ESS was examined using the χ^2 test. An enter-method multivariable logistic regression model was used to estimate the effect of intermediate chronotype and increased daytime sleepiness in HT, with triglycerides, iron, TPOAb, TgAb, and fT3 included as covariates, and age, BMI, and LT4 therapy adjusted for. For each model, the Nagelkerke R^2 was calculated, and multicollinearity was assessed. Nagelkerke R^2 values closer to one indicate better model fit; values below 0.2 indicate a weak relationship between the predictors and the outcome, values between 0.2 and 0.4 reflect a moderate relationship, and values above 0.4 indicate a strong relationship. The variance inflation factor (VIF) was used to detect multicollinearity in the regression analysis. A VIF value of 5 to 10 indicates potential multicollinearity,[49] suggesting dependence among multiple independent variables in the model and possibly affecting the interpretation of the regression results. A sensitivity analysis was conducted in JASP (version 0.18.3, Amsterdam, Netherlands) using the regression method with a confusion matrix.[50] The significance level was set at two-sided $P < 0.05$, and all P values were adjusted using the Bonferroni test for multiple comparisons.

Results

The mean age was 43 ± 12 years, with the youngest woman being 19 years old and the oldest 72 years old. A normal BMI was observed in 57 (53.8%) women, overweight in 28 (26.4%) women, and obesity in 21 (19.8%) women. Elevated cholesterol levels were found in 64.2% (n = 68) of women, while elevated triglyceride levels were found in 17 (16%) women. Reduced HDL levels were recorded in 13 (12.3%) women, and elevated LDL levels in 26 (24.5%) women. Decreased vitamin D levels were detected in 40 (37.7%) women, and reduced iron levels in 15 (14.2%) women. Only one woman had a normal TPOAb level (<34 kIU/L); elevated TPOAb levels were measured in 105 (99.1%) women. Normal TgAb levels (up to 115 kIU/L) were found in 27 (25.5%) women, while 79 (74.5%) women had elevated TgAb levels. All women had elevated TSH levels; one had reduced fT3 levels, and nine had reduced fT4 levels. A total of 65 (61.3%) women were receiving hormone replacement therapy with LT4.

The association of general and biochemical data with chronotype and daytime sleepiness is presented in Table 1. Among the general parameters, only age was significantly associated with chronotype (χ^2 = 467.677; P = 0.026). A significant association was observed between TgAb levels and both chronotype and daytime sleepiness, as well as between TSH levels and daytime sleepiness.

The majority of women (61.3%) exhibited an intermediate chronotype, while 40 women (37.7%) had an evening chronotype, and only one woman (0.9%) had a morning chronotype. The woman with a morning chronotype was excluded from further chronotype analyses. Women were divided into two groups based on chronotype, and differences were examined between those with intermediate and evening chronotypes.

Differences in biochemical parameters of thyroid function by chronotype are presented in Table 2. Women with intermediate chronotypes had significantly lower fT3 levels than those with evening chronotypes. Other biochemical parameters did not differ by chronotype. Both evening and intermediate chronotypes were similar in age and BMI.

Table 2. Differences in biochemical parameters of thyroid function according to chronotype (N = 105)

Variable	Evening (n = 40)	Intermediate (n = 65)	*P**	Effect size
Age (years)	41 (37–50.25)	41 (33–50)	0.577	0.065
BMI (kg/m^2)	25.07 (22.14–29.28)	24.43 (22.03–28.67)	0.727	0.041
Cholesterol (mmol/L)	5.20 (4.48–5.90)	5.50 (4.50–6.00)	0.524	−0.075
Triglycerides (mmol/L)	1.30 (0.98–1.50)	1.20 (0.90–1.60)	0.706	−0.044
HDL (mmol/L)	1.55 (1.40–1.83)	1.50 (1.30–1.90)	0.624	0.057
LDL (mmol/L)	2.25 (1.60–3.03)	2.10 (1.60–2.90)	0.932	−0.010
Iron (µmol/L)	12.00 (8.00–18.00)	15.50 (9.00–21.00)	0.125	−0.179
Vitamin D (nmol/L)	57.75 (43.83–81.35)	56.70 (43.00–73.00)	0.744	0.038
TPOAb (kIU/L)	237.20 (101.75–397.88)	265.50 (127.00–690.00)	0.300	−0.121
TgAb (kIU/L)	157.50 (120.13–211.38)	190.40 (100.50–330.00)	0.199	−0.150
TSH (mU/L)	9.90 (7.70–12.58)	11.60 (8.20–17.70)	0.127	−0.178
fT3 (pmol/L)	5.65 (5.03–6.18)	5.30 (4.50–5.80)	0.043	0.236
fT4 (pmol/L)	16.15 (14.53–17.78)	15.00 (13.30–17.30)	0.098	0.193

**P*-values for the Mann–Whitney U test. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TPOAb, thyroid peroxidase antibodies; TgAb, thyroglobulin antibodies; TSH, thyrotropin; fT3, free triiodothyronine; fT4, free thyroxine. Data are presented as median (IQR).

A logistic regression model was constructed to estimate the independent effects of biochemical analytes across two chronotype categories, using the evening chronotype as the reference. The model showed that women with intermediate chronotype had significantly lower fT3 levels ($P = 0.045$; OR = 0.500; 95% CI 0.25–0.98) but higher iron levels ($P = 0.037$; OR = 1.073; 95% CI 1.01–1.15), as presented in Table 3. VIFs for this model ranged from 1.044 to 1.642, indicating no multicollinearity between chronotype categories and any other variable in the model; therefore, multicollinearity does not affect the interpretation of the regression results. The Nagelkerke R^2 for the model was 0.196, indicating that the regression model explains 19.6% of the variance in chronotype. The model sensitivity was 83.1%, and the specificity was 42.5%.

Most women were in the normal daytime sleepiness category (68.9%), while the fewest were in the severe daytime sleepiness category (3.8%). The mild and moderate daytime sleepiness categories included 20 (18.9%) and 9 (8.5%) women, respectively. Based on self-reported daytime sleepiness, differences were analyzed between women with normal and increased daytime sleepiness, with the latter comprising the mild, moderate, and severe categories as defined by the ESS.

Table 3. Odds ratios for women with intermediate chronotype, adjusted for risk factors

Variable	Beta	SE	OR (95% CI)	*P*
Iron (µmol/L)	0.071	0.034	1.073 (1.01–1.15)	0.037
TPOAb (kIU/L)	0.000	0.001	1.000 (0.99–1.01)	0.587
TgAb (kIU/L)	0.003	0.002	1.003 (1.00–1.01)	0.082
TSH (mU/L)	−0.028	0.070	0.973 (0.85–1.12)	0.691
fT3 (pmol/L)	−0.692	0.346	0.500 (0.25–0.98)	0.045
fT4 (pmol/L)	−0.056	0.159	0.945 (0.69–1.29)	0.723

Adjusted for age, BMI, and LT4 therapy. BMI, body mass index; CI, confidence interval; fT3, free triiodothyronine; LT4, levothyroxine; OR, odds ratio; SE, standard error; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; TSH, thyrotropin.

No significant differences in thyroid hormone or antibody parameters were observed between women with HT and normal or increased daytime sleepiness, although iron levels differed between groups (Table 4). The normal and increased daytime sleepiness groups were also similar in age and BMI.

A logistic regression model was constructed to assess the independent effects of biochemical analytes on daytime sleepiness categories, using normal sleepiness as the reference. Women with increased daytime sleepiness had significantly higher levels of TgAb ($P = 0.049$; OR = 1.003; 95% CI 1.00–1.01) and iron ($P = 0.027$; OR = 1.080; 95% CI 1.01–1.16), as shown in Table 5. VIF values ranged from 1.095 to 5.350, suggesting no severe multicollinearity, although one value exceeded 5 and should be interpreted with caution. The Nagelkerke R^2 for the model was 0.170, indicating that the regression model explains 17% of the variance in daytime sleepiness. The model sensitivity was 30.3%, and the specificity was 91.8%.

Discussion

In the present study, 61.3% of women with HT had an intermediate chronotype, while the evening chronotype accounted for 37.7%, and the morning chronotype was observed in only 0.9% of women. Furthermore, 68.9% of women reported normal daytime sleepiness.

Chronotype was significantly associated with age ($P = 0.026$) and TgAb levels ($P = 0.012$), whereas daytime sleepiness was significantly associated with TgAb ($P = 0.016$) and TSH levels ($P = 0.040$). The logistic regression model showed that fT3 levels were significantly lower in women with an intermediate chronotype compared to those with an evening chronotype ($P = 0.045$). Women with increased daytime sleepiness had significantly higher TgAb levels ($P = 0.049$) compared to those with normal daytime sleepiness.

The distribution of chronotypes observed in this study may have influenced the interpretation of the results. It should be noted

Table 4. Differences in thyroid function biochemical parameters according to daytime sleepiness (N = 106)

Variable	Normal sleepiness (n = 73)	Increased sleepiness (n = 33)	*P**	Effect size
Age (years)	41 (35–53)	40 (31–48)	0.202	0.156
BMI (kg/m^2)	24.24 (21.87–28.40)	25.49 (22.42–29.53)	0.371	−0.109
Cholesterol (mmol/L)	5.50 (4.80–6.00)	5.20 (4.10–5.90)	0.191	0.159
Triglycerides (mmol/L)	1.30 (1.00–1.60)	1.20 (0.90–1.50)	0.591	0.066
HDL (mmol/L)	1.50 (1.40–1.80)	1.60 (1.30–1.90)	0.639	−0.057
LDL (mmol/L)	2.30 (1.70–3.10)	2.00 (1.10–2.87)	0.148	0.176
Iron (µmol/L)	14.00 (9.00–18.00)	17.00 (11.00–23.00)	0.044	−0.245
Vitamin D (nmol/L)	58.00 (43.00–73.30)	56.50 (43.00–73.30)	0.819	0.028
TPOAb (kIU/L)	270.50 (132.50–541.00)	250.00 (102.20–755.00)	0.973	0.004
TgAb (kIU/L)	157.00 (100.25–230.00)	200.00 (142.25–325.90)	0.249	−0.232
TSH (mU/L)	10.80 (7.80–15.30)	11.40 (8.80–16.60)	0.493	−0.083
fT3 (pmol/L)	5.40 (4.60–5.95)	5.60 (4.50–6.00)	0.411	−0.100
fT4 (pmol/L)	16.00 (13.65–17.80)	14.90 (13.70–16.65)	0.392	0.104

**P*-values for the Mann–Whitney U test. BMI, body mass index; fT3, free triiodothyronine; fT4, free thyroxine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; TSH, thyrotropin. Data are presented as median (IQR).

that a previous study of women with hypothyroidism reported a much higher prevalence of morning chronotype compared to evening chronotype, 56% vs. 6%.[51] Although these results differ from ours, the potential influence of inclusion criteria should be considered. The mean age of women in Arosemena *et al*.[51] was 56.5 ± 7 years, whereas the women in the present study were younger, with a mean age of 43 ± 12 years. The age-related shift in chronotype likely explains the predominance of different chronotypes in these studies, as older individuals are more likely to show a morning preference.[52] The observed differences may also be explained by the use of different questionnaires (MCTQ vs. MEQ) and exclusion criteria, such as shift work and sleep apnea.

Additionally, all women in the study by Arosemena *et al*.[51] were on LT4, whereas in the present study, only 61.3% were receiving hormone replacement therapy. In individuals with HT, an evening chronotype is more frequently observed, likely due to daytime fatigue and reduced energy levels,[51] as well as relatively better alertness in the evening. These effects may be related to altered hormonal regulation and inflammatory processes characteristic of autoimmune disease. Inflammatory processes can trigger a vicious cycle of immune responses, disrupting circadian rhythms.[53–55] The prevalence of chronotypes in a Croatian population of 200 healthy controls, including both men and women, six of whom had thyroid disease, was 1% for evening chronotype, 50.5% for intermediate chronotype, and 48.5% for morning chronotype, based on the full MEQ scale.[47] However, when the rMEQ cutoffs used in this study are applied, the distribution remains approximately the same: 4% evening chronotype, 45.5% intermediate, and 50.5% morning chronotype. This chronotype distribution differs significantly from that observed in this sample of women with HT.

A study of 1,097 Finnish participants showed that women with an evening chronotype had a significantly greater increase in body weight and BMI over seven years compared to those with a morning chronotype, partially mediated by depressive symptoms.[56] However, we did not find an association between chronotype and BMI in women with HT. A study of chronotypes in women with hypothyroidism found that lower BMI was associated with a higher likelihood of a morning chronotype, but there was no

Table 5. Odds ratios for women with increased daytime sleepiness adjusted for risk factors

Variable	Beta	SE	OR (95% CI)	*P*
Cholesterol (mmol/L)	−0.310	0.326	0.733 (0.38–1.39)	0.341
LDL (mmol/L)	0.014	0.318	1.014 (0.54–1.89)	0.965
Iron (µmol/L)	0.077	0.035	1.080 (1.01–1.16)	0.027
TPOAb (kIU/L)	−0.000	0.001	1.000 (0.99–1.01)	0.959
TgAb (kIU/L)	0.003	0.002	1.003 (1.00–1.01)	0.049
TSH (mU/L)	−0.066	0.073	0.936 (0.91–1.08)	0.367
fT3 (pmol/L)	0.374	0.391	1.453 (0.68–3.12)	0.339
fT4 (pmol/L)	−0.166	0.164	0.847 (0.61–1.17)	0.313

Adjusted for age, BMI, and LT4 therapy. BMI, body mass index; CI, confidence interval; fT3, free triiodothyronine; LT4, levothyroxine; OR, odds ratio; SE, standard error; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; TSH, thyrotropin.

significant difference in BMI between intermediate and evening chronotypes.[51] Additionally, women with an evening chronotype experienced greater weight gain and had a higher BMI than those with a morning chronotype.[56] Furthermore, a meta-analysis found that individuals with an evening chronotype had a higher BMI than those with a morning chronotype.[57] However, a study of 110 healthy volunteers aged 35 to 75 years, with a mean age of 56.2 ± 15.8, found that evening and morning chronotypes had similar BMIs, although morning chronotypes were associated with a lower BMI.[58] This is consistent with the results of the present study, which showed that women with evening and intermediate chronotypes had similar BMIs and that chronotype was not associated with BMI.

A study conducted in Ukraine among healthy volunteers found that individuals with morning chronotypes were significantly older than those with evening chronotypes.[58] However, a study by Arosemena *et al*.[51] in women with hypothyroidism found no age difference between morning and evening, nor intermediate and evening chronotypes, which is consistent with the present study, where evening and intermediate chronotypes were similar in age.

A significant difference in fT3 levels was observed between women with intermediate chronotypes and those with evening chronotypes, with the latter group having higher fT3 values (P = 0.045). In HT, fT3 levels may be reduced, which can substantially affect alertness. Free T3 accelerates metabolism and promotes cellular energy production[59]; therefore, lower fT3 levels result in slower metabolism, increased fatigue, and a tendency to go to bed earlier,[60] findings consistent with those of the present study.

Increased sleep disturbances are common in individuals with subclinical hypothyroidism[39]; however, 68.9% women in this study had normal daytime sleepiness. Mendelian randomization studies using UK Biobank population samples produced inconclusive results on the relationship between hypothyroidism and daytime sleepiness.[34,61] Wang *et al*.[34] found no association between hypothyroidism and daytime sleepiness in 452,071 individuals, whereas Jia *et al*.[61] observed a potential link between hypothyroidism and daytime sleepiness. A cross-sectional study demonstrated an association between impaired thyroid function and increased daytime sleepiness, particularly in obese women.[62] Nevertheless, although this study may provide valuable insights into exposure and daytime sleepiness, the cross-sectional design limits causal inference.[63]

Pekgör *et al*.[64] conducted a case-control study in Turkey examining the association between daytime sleepiness, assessed by the ESS questionnaire, in 75 patients with hypothyroidism and 52 healthy controls, and found no significant difference between the groups. However, significant differences in lipid profiles were observed in relation to daytime sleepiness among patients with hypothyroidism. Patients with increased daytime sleepiness and hypothyroidism had higher levels of total cholesterol, HDL, and LDL. Differences in TSH and fT4 were not significant between patients with hypothyroidism and increased daytime sleepiness and those with normal daytime sleepiness.[64]

Homeostatic mechanisms interconnect sleep and the HPT axis. This relationship is bidirectional: sleep regulates HPA activity, while HPA hormones influence sleep. Sleep duration and quality affect the circadian rhythms of TSH and thyroid hormone secretion,[34,65] and this secretion persists even in the absence of the SCN.[66,67] In the present study, TSH was associated with daytime sleepiness (P = 0.040). Zheng *et al*.[68] conducted a two-way Mendelian randomization study. Forward analysis showed that increased daytime sleepiness and prolonged sleep duration were negatively correlated with fT3 and fT4 levels, respectively. In contrast, insomnia was negatively correlated with TSH levels. Reverse Mendelian randomization indicated that lower fT3 and higher TSH levels were associated with an increased risk of sleep apnea, with elevated TSH potentially contributing to a stronger morning preference.[68] Elevated TSH, characteristic of HT, may increase daytime sleepiness, whereas reduced TSH in hyperthyroidism enhances morning alertness. Low thyroid hormone levels can slow metabolism, leading to fatigue and daytime sleepiness. Conversely, chronic sleep deprivation can disrupt the rhythms of TSH secretion,[21,69] and circadian misalignment can negatively affect the endocrine system.[21,70,71] Sleep deprivation may increase sleepiness and alter HPT axis function, leading to increased TSH secretion.[39,72,73] In contrast, acute sleep restriction results in a significant decrease in TSH.[34,72] The relationship between thyroid hormones and the sleep cycle is not entirely understood[34]; nonetheless, hypothyroidism symptoms, including insomnia, are frequently observed.[61] Elevated thyroid hormone levels are associated with shorter sleep durations, and it is hypothesized that the increase in T4 following sleep loss represents an adaptive response to promote wakefulness.[31,34]

Although TgAb alone is not directly associated with daytime sleepiness, it is a marker of active autoimmunity and systemic inflammation. In this study, TgAb levels are associated with increased daytime sleepiness (P = 0.016) and chronotype (P = 0.012). Elevated TgAb levels may indicate increased inflammation, which can reduce energy and promote fatigue. An animal study showed that circadian disruption stimulates lymphocytic infiltration of the thyroid and increases TgAb and cytokine production.[66] Elevated TgAb levels may be associated with more severe disease and hormonal imbalance.[66,74] These findings point to an interdependence between circadian rhythm disturbances and hypothyroidism. Sleep and the immune system are interconnected through the regulation of cytokine balance and circadian mechanisms. Chronic sleep deprivation or circadian rhythm disruption can increase inflammatory activity and affect immune function, including the production of autoantibodies.[75] Previous epidemiological studies have shown that insufficient sleep may be associated with a higher likelihood of elevated TPOAb levels in euthyroid individuals. However, continuous TPOAb levels did not show a linear association with sleep parameters.[75] Furthermore, Shimizu *et al*.[75] found no specific association between TPOAb levels and insufficient sleep in euthyroid women. Analysis of NHANES data from the general population, including 6,919 subjects, showed that positive TgAb was associated with longer sleep duration and sleep disturbances, even after adjustment for potential confounders. However, this statistical significance for positive TPOAb was lost after adjustment for potential confounders.[24] These findings support our results suggesting that TgAb may be associated with sleep patterns and circadian preferences, potentially through circadian and immune mechanisms. Mechanistically, circadian disruption and immune activation targeting specific autoantigens may differentially modulate autoantibody generation, with the immunomodulatory effects of sleep disturbances potentially influencing TgAb production more strongly than TPOAb.[66] Additionally, genetic and immunological differences in the regulation of responses to TgAb and TPOAb,[76,77] further support the observed differences in the association of these autoantibodies with sleep parameters and chronotype.

Advantages of the study

The study's main advantage was that the sample was relatively

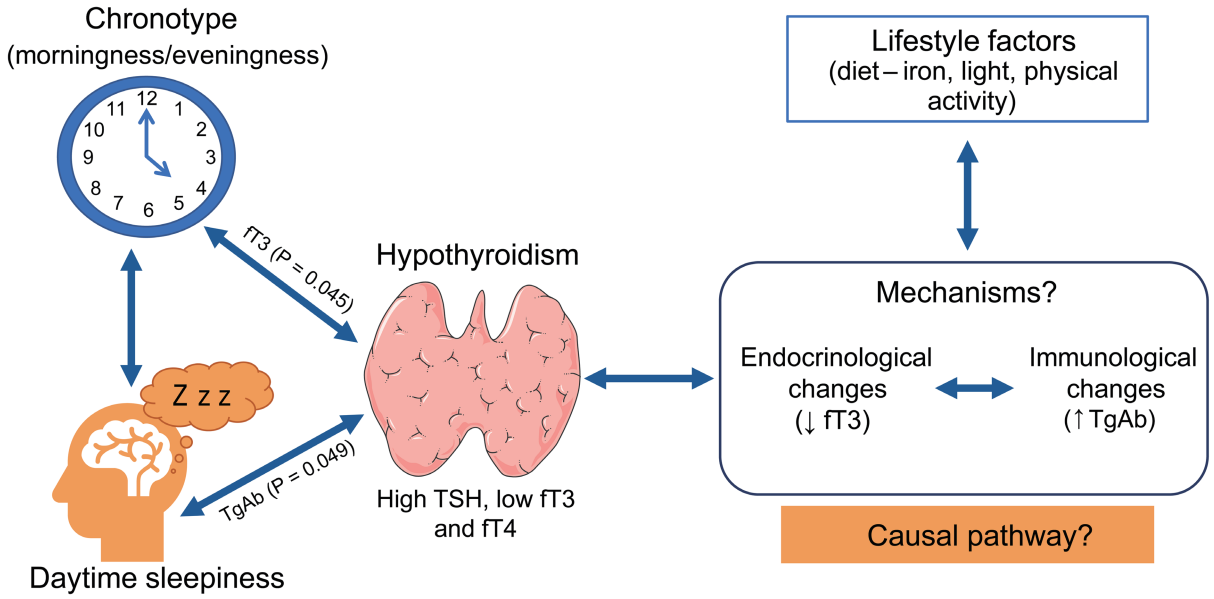

Fig. 2. Fig. 2. Interconnections among thyroid function, chronotype, and daytime sleepiness: potential pathways. This figure shows potential pathways and directions for further research on the relationships among thyroid function, chronotype, and daytime sleepiness. Some studies, including this one, have found that lower fT3 levels are associated with earlier bedtimes or an earlier chronotype.[60] Daytime sleepiness in the present study, as well as sleep disturbances in various studies, has been associated with TgAb.[66] fT3, free triiodothyronine; fT4, free thyroxine; TgAb, thyroglobulin antibodies; TSH, thyroid-stimulating hormone (thyrotropin).

homogeneous in terms of age, ethnicity, and social background.

Study limitations

This study has several limitations. First, the sample size was limited; however, an appropriate sampling frame was feasible only during routine clinical procedures within a single medical institution, which may limit external validity. This sample size may have affected precision and reliability and increased variability. Second, by using questionnaires to assess chronotypes and daytime sleepiness, women provided subjective evaluations of their circadian rhythm. The assessment would have been more objective if the duration and quality of each woman's sleep had been digitally recorded. The woman with a morning chronotype was excluded as an outlier from further chronotype analyses, but the results remained the same with or without her data. Additionally, data on shift work and recent jet lag were not collected, which can substantially affect outcomes related to chronotype and daytime sleepiness. A significant proportion of women were overweight, which could have affected the results, as could any undiagnosed sleep disorders. This study did not exclude women taking sleeping pills, nor did it account for alcohol or coffee intake. Changes in sleep preferences associated with aging may have contributed to early morning awakenings. However, even after controlling for age in the statistical models, the results did not change significantly. Light exposure and BMI may affect chronotypes in women with hypothyroidism,[51] and sunlight is important in the sleep–wake cycle. Studies have shown that people living at higher latitudes tend to have more evening chronotypes,[78,79] which may explain the higher proportion of evening chronotypes than morning chronotypes in this study. Third, because exposure and outcome are assessed simultaneously in cross-sectional studies, this study design provides minimal information for causal inference. Nevertheless, despite methodological limitations, it can provide useful insight into potential causal effects of disease exposures.[63] Therefore, methodologically rigorous longitudinal studies are required to thoroughly elucidate the complex interrelationships among thyroid function, chronotype, daytime sleepiness, TgAb, and fT3 in individuals with HT.

Future directions

Observed associations can indicate a potential causal relationship between chronotype, daytime sleepiness, and hypothyroidism.[61] However, no study has thoroughly investigated or clearly defined the mechanisms by which reduced thyroid hormone levels may influence chronotype and daytime sleepiness. Future research should focus on elucidating how autoimmune thyroid activity, particularly elevated TgAb levels, modulates circadian rhythm and daytime sleepiness. Longitudinal studies would provide stronger evidence for causality and clarify the role of fT3 in chronotype (Fig. 2). Moreover, the implementation of objective sleep measures, such as actigraphy, alongside endocrinological and immunological parameters could help develop more precise models for predicting clinical outcomes. A translational research approach may enable the design of personalized therapeutic strategies that consider chronotype, autoimmune status, and hormonal status to optimize hypothyroidism treatment. Additionally, exploring gene–environment interactions and the impact of lifestyle factors on these relationships could further enhance our understanding and inform targeted interventions.

Conclusions

Approximately one-third of women have an evening chronotype and approximately one-third had increased daytime sleepiness. TgAb, fT3, and TSH are associated with daytime sleepiness or chronotype in women with HT. Further investigation is required for the underlying mechanisms.

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Conflict of interest

IŠ has been an editorial board member of *Exploratory Research and Hypothesis in Medicine* since November 2021. SD is a current employee of DNA Laboratory, Genos Ltd., Zagreb. The authors have no other conflicts of interest to report.

Author contributions

Statistical analysis (ZB, IŠ), data interpretation (ZB, IŠ), literature review (ZB, SD, DK, DL, MB, IŽ, NG, IŠ), drafting of the manuscript (ZB, IŠ), revision of the manuscript (ZB, SD, DK, DL, MB, IŽ, NG, IŠ), data collection (SD, DK, DL, MB, IŽ, NG), study conceptualization, study design, and study supervision (IŠ). All authors approved the final version of the manuscript.

Ethical statement

This study was approved by the Ethics Committee of the Leptir Polyclinic Zagreb (No. 25-10-6-12/23) and the Ethics Committee of the Faculty of Dental Medicine and Health, Osijek, Josip Juraj Strossmayer University, Osijek, Croatia (No. 2158/97-97-10-24-03). All patients signed written informed consent agreeing to complete the questionnaire and allow the use of their medical data (e.g., biochemical analytes) for the study. The study was conducted in accordance with the principles of good clinical practice, the Declaration of Helsinki, its 2013 revision, and all subsequent amendments.

Data sharing statement

The data used in support of the findings of this study are available from the corresponding author at iskrlec@fdmz.hr upon request.

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